This Week in The Journal

KCTD Proteins Enable GABAergic Excitation of Habenular Axons

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(see pages 1648–1665)

Cholinergic neurons projecting from the medial habenula (MHb) to the interpeduncular nucleus (IPN) corelease glutamate and regulate the activity of downstream neurons that regulate behaviors associated with drug withdrawal and fear learning. The presynaptic terminals of MHb axons in the IPN express GABA_B receptors (GABA_BRs), and, remarkably, activation of these receptors enhances, rather than inhibits, neurotransmitter release. How this unusual effect is produced is unclear, but it has been hypothesized that K⁺ channel tetramerization domain (KCTD) proteins are involved. These proteins promote surface expression of GABA_BRs and help create a scaffold that links the receptors to effector G-proteins and ion channels. Consistent with this hypothesis, recent work showed that KCTD8 binds to and enhances current through R-type calcium channels in MHb axon terminals (Bhandari et al., 2021, *eLife* 10:e68274). Ren et al. extend these findings by showing that KCTD8 and KCTD12 enhance expression of GABA_BRs in MHb axon terminals.

Consistent with previous work, electrical stimulation in the IPN increased calcium levels in the presynaptic terminals of MHb axons, and this effect was potentiated by the GABA_BR agonist baclofen. Furthermore, photostimulation of channelrhodopsin-expressing MHb axons in the IPN evoked EPSCs in postsynaptic neurons, and baclofen increased EPSC amplitude. These effects were present in mice lacking both KCTD8 and KCTD12, but the effect of baclofen was significantly reduced in these mice. The reduced effect of baclofen likely stemmed from the fact that GABA_BR expression in presynaptic terminals of MHb axons was reduced in KCTD8/12-deficient mice. Notably, reintroducing either KCTD8 or KCTD12 was sufficient to rescue GABA_BR expression and baclofen effects in KCTD8/12-deficient mice, and conversely, knocking out just one

of these proteins did not affect GABA_BR levels or function. Finally, knocking out KCTD8/12 reduced the ability of baclofen to facilitate extinction of learned fear behavior in mice.

These results suggest that KCTD8 and KCTD12 have redundant functions in promoting the expression of GABA_BR expression in—and thus GABA-mediated excitation of—MHb axon terminals in the IPN. In contrast, KCTD8/12 knockout did not alter GABA_BR expression or the inhibitory effect of baclofen in the cell bodies of MHb neurons, indicating that these proteins can selectively regulate GABA_BR expression and function in particular subcellular compartments.

Electrical stimulation in the IPN increases calcium levels, as revealed by a fluorescent indicator. This effect is enhanced by baclofen (right panels), but the effect of baclofen is smaller in mice lacking KCTD8 and KCTD12 (bottom) than in wild-type mice (top). See Ren et al. for details.

Adenosine Tonicly Inhibits Dopamine Release in the Striatum

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(see pages 1738–1751)

Dopamine release in the striatum is essential for learning, choosing, and performing goal-directed action. Whereas tonic dopamine release regulates response vigor given current reward values, phasic bursts of dopamine are thought to signal unexpected rewards and stimuli that predict them. How much dopamine is released with each

action potential is regulated within the striatum by glutamate, GABA, acetylcholine, and adenosine. Receptors for these modulators are present on many cell types, creating a complex regulatory network. For example, adenosine inhibits acetylcholine release from cholinergic interneurons, and thus reduces cholinergic regulation of dopamine release. Roberts et al. report that adenosine also acts directly on dopaminergic axons to reduce dopamine release. Intriguingly, this effect is regulated by astrocytes.

Application of an adenosine A1 receptor (A1R) agonist reduced dopamine release evoked by either photostimulation of channelrhodopsin-expressing dopaminergic axons or electrical stimulation in the striatum. Importantly, antagonists of GABA and nicotinic acetylcholine receptors did not reduce this effect. In contrast, A1R antagonists increased striatal dopamine release, suggesting that dopamine release is tonically suppressed by adenosine. Intriguingly, activation of A1Rs reduced dopamine release evoked by low-frequency stimulation to a greater extent than it reduced release evoked by high-frequency stimulation, suggesting that adenosine tone can modulate the difference in dopamine release produced by tonic versus phasic firing.

As a breakdown product of ATP, adenosine is present extracellularly throughout the brain. Astrocytes take up adenosine via equilibrative nucleoside transporter type 1 (ENT1), and thus can regulate activation of A1Rs. Inhibiting ENT1 with selective antagonists or with ethanol increased extracellular adenosine levels in the striatum, reduced evoked dopamine release, and increased the effect of A1R antagonist. Conversely, overexpressing ENT1 in astrocytes increased the amount of dopamine released during optogenetic stimulation.

These data suggest that striatal astrocytes can regulate the contrast between tonic and phasic dopamine signaling by taking up adenosine via ENT1. This adds to previous work showing that astrocytes limit tonic inhibition of dopamine release by taking up extracellular GABA and glutamate, further highlighting the essential role of striatal astrocytes in reward processing, motivation, and action selection.

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